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(54) Title: METHODS OF MODULATING URIC ACID LEVELS

(57) Abstract

The invention provides methods for the treatment of diseases associated with hyperuricemia by administering to a subject in need of such treatment, an effective amount of a high affinity PPARγ ligand.

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METHODS OF MODULATING URIC ACID LEVELS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/116,392, filed January 19,1999.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

Not applicable.

FIELD OF THE INVENTION

The present invention relates to the methods for treating gout and related conditions associated with elevated plasma levels of uric acid, using compounds which have been identified as peroxisome proliferator-activated receptor γ modulators.

BACKGROUND OF THE INVENTION

Urate oxidase (or uricase) is a purine metabolic enzyme that catalyzes the conversion of uric acid to allantoin. The loss of urate oxidase in man during primate evolution predisposes humans to hyperuricemia, a metabolic disturbance that may lead to gout. The term gout encompasses a variety of disorders that include, either alone or in combination, (1) hyperuricemia, (2) attacks of acute inflammatory arthritis, (3) tophaceous deposition of urate crystals in and around joints, (4) deposition of urate crystals in renal parenchyma, and (5) urolithiasis. Hyperuricemia, however, is the key feature of gout and is a result of either an increased production of urate or a decreased excretion of uric acid, or potentially a combination of both processes. Additionally, the increased levels of urate in the plasma or extracellular fluids, then leads to precipitation of urate crystals and tissue deposition of urate, leading to other manifestations of gout noted above. Further, correction of asymptomatic hyperuricemia thereby prevents pathologies associated with long term damage to osteo-articular, renal and vascular systems.

Urate production is influenced by the dietary intake of purines (the metabolism of which leads to uric acid), de novo biosynthesis of purines from nonpurine

precursors, nucleic acid turnover and salvage (or conversion) of free purine bases to nucleotides by phosphoribosyltransferase activities.

Defects in renal handling of uric acid, however, is implicated in approximately 98 percent of individuals with hyperuricemia. Typically, this is due to reduced glomerular filtration of urate or decreased tubular secretion of urate.

The effective treatment of gout may be achieved only by a stable and chronic lowering of the patient's serum urate level. Reduction of serum uric acid below the saturation level of 6.4 mg/dL may involve any of several therapeutic strategies. The use of uricosuric agents increases the excretion of uric acid thereby reducing the plasma concentration, and is of use in about 80% of affected patients who suffer some impairment in normal renal excretion of waste product. Among these, probenecid, sulfinpyrazone and benzbromarone are the best known. The use of sulfinpyrazone is limited by the appearance of blood dyscrasias, which lead to discontinuation of therapy in about 25% of patients. Additionally, sulfinpyrazone and probenecid may cause gastrointestinal irritation in some patients and induce paradoxical uric acid retention when administered in low doses. Other strategies include the use of xanthine oxidase inhibitors (*e.g.*, allopurinol and tisopurine). The use of these enzyme inhibitors results in decreased production of uric acid, but are also associated with side effects sufficiently severe to often warrant discontinuation of therapy, including induction of hypersensitivity and adverse drug-drug interactions.

Benzbromarone has been shown to be a potent inhibitor of renal urate absorption. The lowering of serum urate levels is mediated by its potent uricosuric activity as demonstrated by the persistent elevation of urinary urate excretion. However, common side effects of clinical treatment include gastro-intestinal disturbances, including diarrhea.

Thus, further investigation into uricosuric agents could provide new therapeutic treatments which provide advantages to existing methods.

SUMMARY OF THE INVENTION

The present invention derives from the surprising discovery that activators of peroxisome proliferator-activated receptor γ (PPARγ) are also uricosuric agents and are useful for the treatment of gout and related disorders.

Accordingly, in one aspect, the present invention provides methods for the treatment of diseases associated with hyperuricemia by administering to a subject in need of such treatment, an effective amount of a high affinity PPARγ ligand, with the proviso that the ligand is other than benzbromarone or sulfinpyrazone.

In one group of embodiments, the high affinity PPARγ ligand is a thiazolidinedione, phenylsulfonamidophenoxypyridine, substituted 4-hydroxyphenylalkanoic acid, isoxazolidine-3,5-dione or a noncyclic 1,3-dicarbonyl analog of an isoxazolidine-3,5-dione. In one group of preferred embodiments, the high affinity PPARγ ligand is a thiazolidinedione selected from the group consisting of ciglitazone, pioglitazone, troglitazone, englitazone, darglitazone, and BRL 49653 (rosiglitazone). In another group of preferred embodiments, the high affinity PPARγ ligand is a substituted phenylsulfonamidophenoxypyridine. In yet another group of preferred embodiments, the high affinity PPARγ ligand is selected from the group consisting of substituted 4-hydroxyphenylalkanoic acids. In still another group of preferred embodiments, the high affinity PPARγ ligand is selected from the group consisting of isoxazolidine-3,5-diones. In yet another group of preferred embodiments, the high affinity PPARγ ligand is selected from the group consisting of noncyclic 1,3-dicarbonyl analogs of isoxazolidine-3,5-diones.

The diseases associated with hyperuricemia are known to those of skill in the art and are described in Goodman & Gilman's Pharmacological Basis of Therapeutic Agents, Ninth Ed., McGraw-Hill, New York, 1996. Preferably, the condition is gout or an inflammatory condition brought about by high levels of uric acid in the joints.

In another aspect, the present invention provides methods for modulating serum uric acid levels in a subject. In this aspect, agents can be administered in a prophylactic manner for prevention, or as treatment for conditions resulting from elevated uric acid levels in a subject. The methods involve administering to a subject, a pharmaceutically acceptable composition comprising a uric acid level modulating amount of a PPARγ ligand other than benzbromarone or sulfinpyrazone. Preferred ligands are those that have been described above.

BRIEF DESCRIPTION OF THE DRAWINGS

The binding activity of a variety of known uricosuric agents to PPARγ is represented in Figure 1. The ability of these compounds to displace the binding of BRL 49653, a known PPARγ ligand, from PPARγ in a radioligand binding assay is demonstrated. The data show that uricosuric agents benzbromarone and sulfinpyrazone are able to displace bound [3H]-BRL 49653 from PPARγ protein, whereas allopurinol, colchicine, indomethacin, phenylbutazone and probenecid do not.

Figure 2 is a bar graph showing the reduction in plasma uric acid concentration achieved using a substituted (phenylsulfonamido)phenoxypyridine (A), an isoxazolidine-3,5-dione (B), and a thiazolidinedione (C). The concentration of uric acid in the plasma after treatment of Zucker obese (fa/fa) rats for a period of seven days is shown. These structurally diverse ligands for PPARγ showed uricosuric activity in this animal model.

Figure 3 provides the structures of certain known PPARγ ligands.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds used in the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds used in the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically

acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds used in the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds used herein may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention can use compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the parent compound. Additionally, prodrugs can be converted to compounds useful in the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to compounds useful in the present invention when placed in a transdermal patch reservoir with a suitable enzyme.

Certain compounds used herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds used in the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Compounds useful herein may also possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and

individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds used in the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

General

The peroxisome proliferator-activated receptors (PPARs) are transducer proteins belonging to the steroid/thyroid/retinoid receptor superfamily. The PPARs were originally identified as orphan receptors, without known ligands, but were named for their ability to mediate the pleiotropic effects of fatty acid peroxisome proliferators. These receptors function as ligand-regulated transcription factors that control the expression of target genes by binding to their responsive DNA sequence (peroxisome proliferator response element) as heterodimers with members of the retinoid-X receptor (RXR) family of transducer proteins. This peroxisome proliferator response element has been reported to occur in the promoter region of genes encoding acyl-CoA synthase, fatty acid binding protein and lipoprotein lipase, which encode enzymes involved in intra- and extra-cellular metabolism lipid and mitochondrial energy metabolism, as well as the differentiation of adiopocytes. PPARs regulate the expression of the *ob*/leptin gene, which is also involved in regulating energy homeostasis as well as adipocyte differentiation. Accordingly, the discovery of transcription factors which link control of lipid metabolism and energy expenditure has provided insight into regulation of energy homeostasis in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes and dyslipidemia

PPARγ is one member of the PPAR nuclear receptor superfamily of ligand-activated transcription factors and has been shown to be expressed in an adipose tissue-enriched manner. Its expression is induced early during the course of differentiation of several pre-adipocyte cell lines. Further, forced expression of PPARγ in fibroblasts results in differentiation of this cell type into adipocytes. Additional research

has now demonstrated that PPARγ plays a pivotal role in the adipogenic signaling cascade.

As part of a screening program to identify ligands for PPARγ, two uricosuric agents were screened and found to bind to PPARγ. In particular, benzbromarone and sulfinpyrazone were each found to be PPARγ ligands. Other uricosuric agents, however, did not bind to PPARγ, including allopurinol, colchicine, indomethacin, phenyl butazone and probenecid (see Figure 1). This discovery led to an evaluation of other PPARγ ligands as potential uricosuric agents. Surprisingly, a broad spectrum of PPARγ ligands were found to also be uricosuric agents, establishing this mechanism as one avenue for the control of gout and other hyperurocemic diseases (see Figure 2). In particular, thiazolidinediones (*e.g.*, troglitazone, darglitazone, ciglitazone, rosiglitazone, and the like), substituted (phenylsulfonamido)phenoxypyridines (*e.g.*, 5-(4-(2,4-dichloro-5-methylphenyl-sulfonamido)-2-carboethoxyphenoxy)-3-chloropyridine (see co-pending application Ser No. 60/073,042 filed January 29, 1998)), and isoxazolidine-3,5-diones and their noncyclic analogs (*e.g.*, JTT-501 and the like, described in Shinkai, *et al., J. Med. Chem.* **41**:1927-1933 (1998)), are shown herein to decrease plasma uric acid levels.

PPARγ is expressed in low abundance in the renal cortex (glomerulus, proximal tubule), but the functional role of this receptor in the kidney is not known. A renal protective action of the PPARγ ligand, rosiglitazone, has been demonstrated in Zucker fatty rats exhibiting a highly exaggerated form of renal disease, where long-term treatment was associated with a marked retardation of progressive nephropathy with proteinuria. Based on these findings, renal PPARγ potentially mediates the uricosuric actions of PPARγ ligands.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

In view of the above surprising discoveries, the present invention provides in one aspect, a method for the treatment of diseases associated with hyperuricemia comprising administering to a subject in need of such treatment an effective amount of a high affinity PPARγ ligand, with the proviso that the ligand is other than benzbromarone or sulfinpyrazone. As used herein, the term "high affinity PPARγ ligand" refers to those

compounds that bind to, and activate PPARγ at a concentration of about 10 micromolar or less using an assay as described in Jiang, et al., Nature 391:82-86 (1998). Alternatively, high affinity PPARγ ligands can be evaluated using the transient cotransfection assay described in Lehmann, et al., J. Biol. Chem. 270(22):12953-12956 (1995), and include those compounds that exhibit activation of PPARγ at a concentration of about 10 μM or less. Biochemical assays (non cell-based) useful for the detection and measurement of PPARγ binding are described in co-pending applications USSN 08/975,614 (filed November 21, 1997) and 09/163,713 (filed September 30, 1998).

While the invention is described using examples of known PPARγ ligands, the breadth of the invention derives from the underlying discovery that PPARγ ligands act as hyperuricemic agents. Accordingly, the methods described herein are applicable to known and even not-yet-discovered PPARγ ligands. For the purpose of illustration, the present invention is described with reference to the known major classes of PPARγ ligands, thiazolidinediones, substituted phenylsulfonamidophenoxypyridines, substituted 4-hydroxyphenylalkanoic acid derivatives (see WO 97/31907) and certain isoxazolidine-3,5-diones (e.g., JTT-501, its derivatives and noncyclic analogs, see Shinkai, et al., J. Med. Chem. 41:1927-1933 (1998)).

As used herein, the term "thiazolidinedione" refers to an entire class of agents which are presently under investigation as antidiabetic agents. These agents have been reviewed in, for example, Whitcomb, *et al., Exp. Opin. Invest. Drugs* **4**:1299-1309 (1995) and Hulin, *et al., Current Pharmaceutical Design* **2**:85-102 (1996) and include not only thiazolidinedione having groups appended at the C-5 position of the thiazolidinedione ring, but also those agents in which the thiazolidinedione ring has been replaced with an isostere having similar activity. A variety of thiazolidinediones have been prepared or developed as potential antidiabetic agents, and are useful in the present invention, for example, ciglitazone, troglitazone, pioglitazone, englitazone, darglitazone and their analogs (see, Hulin, *et al., Curr. Pharm. Design* **2**:85-102 (1996)). Preparation of the thiazolidinediones are described in references cited in Hulin, *et al., ibid.* and in a number of United States patents, including U.S. Patent Nos. 5,811,439, 5,489,602, 5,441,971, 4,775,687, 4,697,020, 4,687,777, and 4,582,839.

Substituted 4-hydroxyphenylalkanoic acid derivatives are also useful in the present invention, and are described in, for example, PCT publication WO 97/31907.

Another group of PPARγ ligands useful in the present invention are the substituted phenylsulfonamidophenoxypyridines, described in co-pending application Ser. No. 60/073,042.

Still another group of PPARγ ligands useful in the present invention are the isoxazolidine-3,5-diones and their noncyclic 1,3-dicarbonyl analogs, described in Shinkai, et al., ibid. As with the thiazolidinedione class of agents, the term "isoxazolidine-3,5-dione" refers to those heterocycles having a group attached at the C-4 position of the ring as well as derivatives and analogs. A number of suitable isoxazolidine-3,5-diones are described in U.S. Patent No. 5,728,720.

In another aspect, the present invention provides methods for modulating serum uric acid levels in a subject, comprising administering to the subject, a serum uric acid modulating amount of a PPARγ ligand other than benzbromarone or sulfinpyrazone. In this aspect, agents can be administered in a prophylactic manner for prevention, or as treatment for conditions resulting from elevated uric acid levels in a subject. Preferred ligands are those that have been described above. While the present invention contemplates use in humans, the invention is not so limited and treatments in each aspect of the invention will also find use in veterinary capacities.

Analysis of compounds

The methods of the present invention can be carried out using essentially any PPARγ ligand. Accordingly, compounds useful for these methods are identified as ligands using methods similar to Lehmann, *et al., ibid.* Those compounds that are particularly useful are high affinity ligands and exhibit an IC_{50} value of about 10 μM or less in a PPARγ ligand binding assay. More preferably, the compounds exhibit an IC_{50} value of about 1 μM or less, with values of 0.05 μM or less being most preferred. IC_{50} values are defined as the concentration of test compounds required to reduce the radiolabel (^{3}H-BRL49653) present by 50%.

Formulation and administration of compounds and pharmaceutical compositions

The invention provides methods of using the subject compounds and compositions to treat disease or provide medicinal prophylaxis for conditions such as gout

and other uric acid disorders (see, for example, Harrison's Principles of Internal Medicine, 13th Ed., Isselbacher, et al., eds., McGraw-Hill, NY, pp. 2079-2087 (1994)). These methods generally involve administering to the host or subject in need of such treatment, an effective amount of the PPARγ ligand or pharmaceutically acceptable compositions of the ligands. As used herein, the term "effective amount" refers to that amount of a compound or composition that produces a desired hyperuricemic result.

The compositions and compounds useful in the present invention and the pharmaceutically acceptable salts thereof can be administered in any effective way such as via oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day.

In one embodiment, the invention provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline or other medium, water, gelatin, an oil, etc. to form pharmaceutically acceptable compositions. The compositions and/or compounds may be administered alone or in combination with any convenient carrier, diluent, etc. and such administration may be provided in single or multiple dosages. Useful carriers include solid, semi-solid or liquid media including water and non-toxic organic solvents.

In another embodiment, the invention provides the subject compounds in the form of a pro-drug, which can be metabolically converted to the subject compound by the recipient host. A wide variety of pro-drug formulations are known in the art.

The compositions may be provided in any convenient form including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, etc. As such the compositions, in pharmaceutically acceptable dosage units or in bulk, may be incorporated into a wide variety of containers. For example, dosage units may be included in a variety of containers including capsules, pills, etc.

The compositions may be advantageously combined and/or used in combination with other anti-gout therapeutic or prophylactic agents, different from the subject compounds. In many instances, administration in conjunction with the subject

compositions enhances the efficacy of such agents. Exemplary hypouricemic agents include: colchicine and its derivatives; allopurinol and its derivatives; probenecid and related benzoic acid derivatives; sulfinpyrazone; phenylbutazone; and benzbromarone (see, Goodman & Gilman's Pharmacological Basis of Therapeutic Agents, Ninth Ed., McGraw-Hill, New York, 1996).

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

This example illustrates the PPARγ assay used to evaluate ligands useful in the present invention.

Materials:

1/ PPARγ-GST fusion protein is prepared according to standard procedures.

2/ [^{3}H]-BRL 49653; 50 Ci/mmol specific activity

3/ Polyfiltronics Unifilter 350 filtration plate

4/ Glutathione-Sepharose beads from Pharmacia: 2x washed in 10x excess of binding buffer (BSA and DTT can be left out).

Method:

1/ Binding buffer (10 mM Tris-HCl, pH 8.0, 50 mM KCl, 10 mM DTT, 0.02% BSA, 0.01% NP-40) is added in 80 µl/well to wells of a filtration plate.

2/ Test compound is added in 10 µl DMSO.

3/ PPARγ-GST fusion protein and [^{3}H]-BRL 49653 are premixed in binding buffer containing 10 mM DTT, added in 10 µl/well, so that the final concentrations are: 1 µg/well PPARγ-GST fusion protein and 10 nM [^{3}H]-BRL 49653. The plate is incubated for 15 minutes.

4/ 1 µl/well glutathione-agarose bead is added in 50 µl binding buffer, and the plate is vigorously shaken for 1 hour.

5/ The plate is washed twice with 200 µl/well binding buffer (BSA and DTT can be left out). This collected as hot waste. Then washed twice more, which is collected as cold waste.

6/ The bottom of the plate is sealed, 200 µl/well scintillation cocktail is added, the top of plate is sealed, and radioactivity is determined.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for modulating serum uric acid levels in a subject, said method comprising administering to said subject a uric acid level modulating amount of a PPARγ ligand other than benzbromarone or sulfinpyrazone.

2. A method in accordance with claim 1, wherein said PPARγ ligand is selected from the group consisting of thiazolidinediones, phenylsulfonamidophenoxypyridines, substituted 4-hydroxyphenylalkanoic acids, isoxazolidine-3,5-diones and noncyclic 1,3-dicarbonyl analogs of isoxazolidine-3,5-diones.

3. A method in accordance with claim 1, wherein said PPARγ ligand is a thiazolidinedione.

4. A method in accordance with claim 1, wherein said PPARγ ligand is an isoxazolidine-3,5-dione.

5. A method in accordance with claim 1, wherein said PPARγ ligand is a noncyclic 1,3-dicarbonyl analog of an isoxazolidine-3,5-dione.

6. A method in accordance with claim 1, wherein said PPARγ ligand is a phenylsulfonamidophenoxypyridine.

7. A method in accordance with claim 1, wherein said PPARγ ligand has an IC_{50} of 10 micromolar or less in a PPARγ ligand binding assay.

8. A method in accordance with claim 1, wherein said PPARγ ligand has an IC_{50} of 1.0 micromolar or less in a PPARγ ligand binding assay.

9. A method in accordance with claim 1, wherein said administering is oral or intravenous.

10. A method in accordance with claim 1, wherein said PPARγ ligand is administered in combination with a second uricosuric agent.

11. A method in accordance with claim 10, wherein said second uricosuric agent is a member selected from the group consisting of allopurinol,

sulfinpyrazone, colchicine, indomethacin, phenylbutazone, probenecid and benzbromarone.

12. A method for the treatment of diseases associated with hyperuricemia comprising administering to a subject in need of said treatment an effective amount of a high affinity PPARγ ligand, with the proviso that said ligand is other than benzbromarone or sulfinpyrazone.

13. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is selected from the group consisting of thiazolidinediones, phenylsulfonamidophenoxy-pyridines, substituted 4-hydroxyphenylalkanoic acids, isoxazolidine-3,5-diones and noncyclic 1,3-dicarbonyl analogs of isoxazolidine-3,5-diones.

14. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is a thiazolidinedione selected from the group consisting of ciglitazone, pioglitazone, rosiglitazone, troglitazone, englitazone, darglitazone, and BRL 49653.

15. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is a substituted phenylsulfonamidophenoxypyridine.

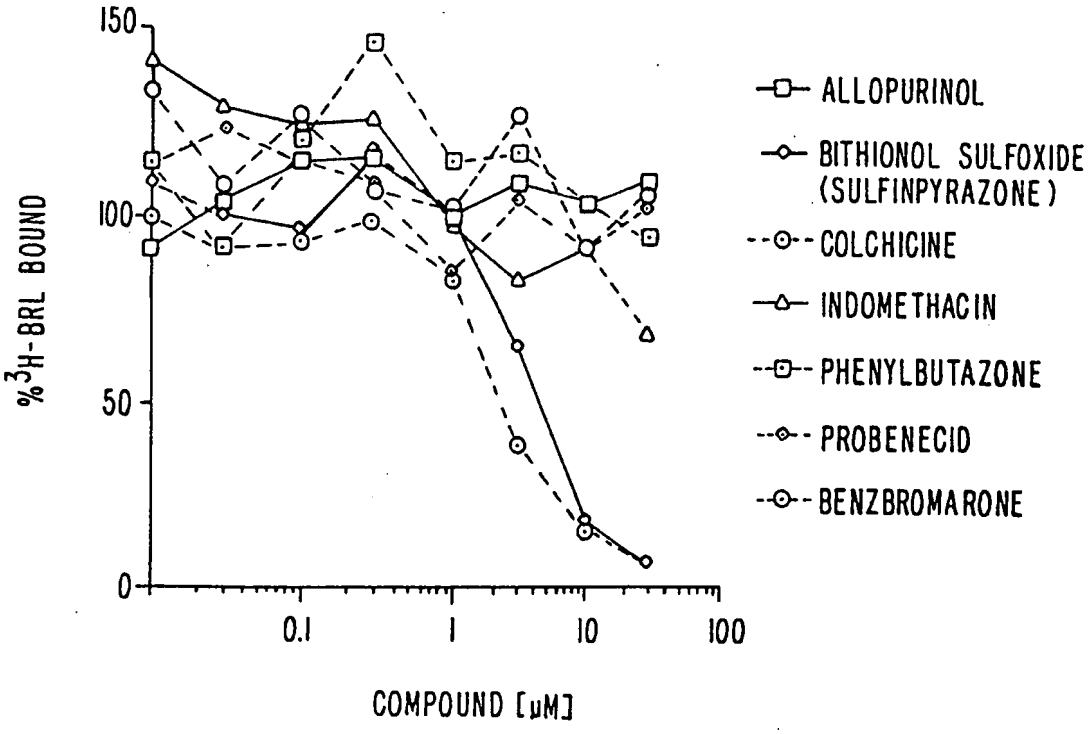
16. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is selected from the group consisting of substituted 4-hydroxyphenylalkanoic acids.

17. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is selected from the group consisting of isoxazolidine-3,5-diones.

18. A method in accordance with claim 12, wherein said high affinity PPARγ ligand is selected from the group consisting of noncyclic 1,3-dicarbonyl analogs of isoxazolidine-3,5-diones.

19. A method in accordance with claim 12, wherein said condition is gout.

20. A method in accordance with claim 12, wherein said condition is an inflammatory condition.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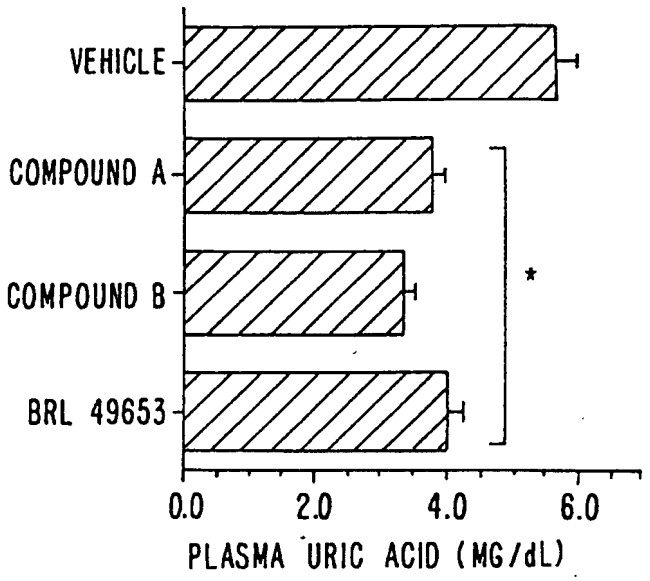
COMPOUND [μM]
ALLOPURINOL
BITHIONOL SULFOXIDE (SULFINPYRAZONE)
COLCHICINE
INDOMETHACIN
PHENYLBUTAZONE
PROBENECID
BENZBROMARONE

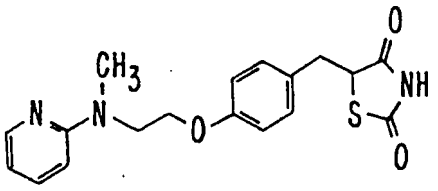
FIG. 1.

COMPOUND A	30 MG/KG IP, BID
COMPOUND B	0.3 MG/KG PO, QD
BRL 49653	10 MG/KG PO, QD

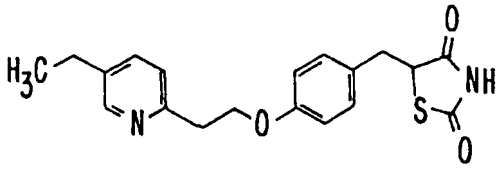


n= 5-6 PER TREATMENT GROUP; * $p < 0.05$ COMPARED TO VEHICLE

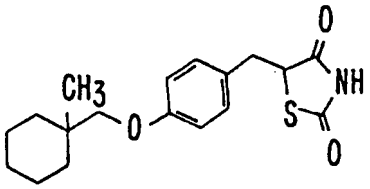
FIG. 2.



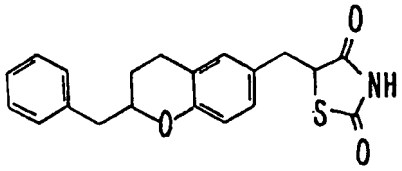
BRL49653



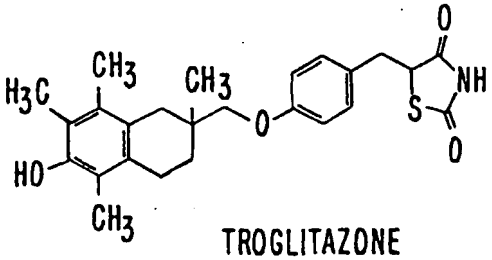
PIOGLITAZONE



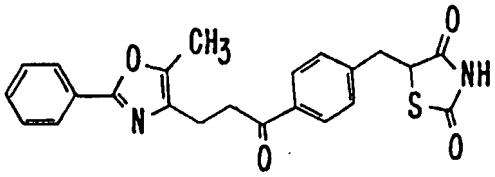
CIGLITAZONE



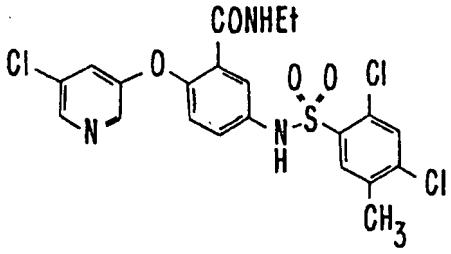
ENGLITAZONE



TROGLITAZONE



DARGLITAZONE



COMPOUND A

FIG. 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01118

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/42
US CL : 514/252, 256, 314, 340, 374
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252, 256, 314, 340, 374

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,728,720 A (SHINKAI) 17 March 1998, see the entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 MAY 2000	Date of mailing of the international search report 24 MAY 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ZOHREH FAY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*